Cocaine: history, use, abuse

Steven B Karch MD

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'. . . spread of morphia and the cocaine habit, is becoming an evil more serious and more deadly than opium smoking, and this evil is certain to increase . . .'—Sir Edward Grey, Foreign Minister, writing to the American Ambassador in London in 1910[1].

Until late in the 1800s, few Europeans even knew that cocaine existed. Cocaine did not become an important business commodity until the scientific foundations of coca growing and cocaine production were established, very late in the nineteenth century. The impact of cocaine abuse on society, not to mention the impact of cocaine use on the death rate, can be accurately related to technical advances in the cocaine trade. The net effect of these advances has been to increase the amount of cocaine that users of this drug can get into their bodies. What follows is a brief description of some of the more important milestones in cocaine technology, and an overview of the most serious medical disorders caused by chronic cocaine use.

All of cocaine's medical complications were originally described in the late 1880s[2–4]. The only difference between then and now is the truly massive scale of today's cocaine industry. Speaking in London in 1987, the psychiatrist Herbert Kleber described the American cocaine epidemic and expressed great concern that the exploding drug supply might eventually wash up on British shores[3]. In the subsequent decade world cocaine production has more than doubled. Even Sir Edward Grey would not have predicted that worldwide production (and consumption) would increase from less than 10 tons in 1910 to more than 700 tons in 1996[3].

THE HISTORY OF COCAINE USE

A century elapsed between the time that Karl Koller announced his discovery that cocaine was an effective local anaesthetic agent and the year (1985) when 'crack' smokers began appearing at medical clinics in the Bahamas[4]. The intervening years had seen important advances in coca cultivation, in cocaine refining, and even in the routes by which cocaine is self-administered. Each technical advance translates into higher blood cocaine concentrations—either because the route of administration is more efficient or simply because there is so much more cocaine available to administer. Either way, chronic exposure to high cocaine concentrations makes the occurrence of adverse events more likely.

Coca has been used by the Amara Indians of Peru for more than 1000 years, but in this group of drug-takers coca-related heart attacks and strokes were, and still are, uncommon. There is a limit to the number of leaves that even the most determined user can chew. The physical constraints of leaf chewing restrict the amount of cocaine that can be introduced into the bloodstream[5], and that acts as a safeguard against toxicity. It would take an enormous amount of coca leaf, and a great deal of chewing, to extract enough cocaine from coca leaves to produce a toxic reaction.

Figure 1 **Coca leaves.** Drawing by Sir William Hooker, 1835, from a specimen collected near Chincheros, Peru. It was later determined that this was a wild variant, not the variety used for commercial coca production. Reproduced from *Companion to the Botanical Magazine* 1835;1:161–5

PO Box 5139, Berkeley, CA 94705, USA

Correspondence to: S B Karch MD
E-mail: fdaa@batnet.com

Figure 2 **Newspaper advertisement for Vin Mariani, London, 1899**

For similar reasons, the practice of drinking coca wines, which were first sold in Europe during the late 1860s, was equally benign. The most famous of these was Vin Mariani. Its formula was proprietary, but the French government guidelines for the manufacture of coca-containing wines were public record, and any pharmacist could make them: 60 g of ground coca leaves were soaked for ten hours in one litre of red or white wine. The only requirement for the wine was that it contained 10–15% alcohol. Given an average cocaine content of ¼–½% for Bolivian leaf (the only kind of leaf available in France at the time), one litre of wine would have contained as little as 150 mg, and certainly no more than 300 mg of cocaine[6]. Two glasses of Mariani's wine would have contained less than 50 mg cocaine, equivalent to one 'line' of snorted cocaine.

Even with today's sophisticated measuring techniques, the 50 mg of cocaine consumed in a glass of coca wine would have been barely enough to cause measurable effects in humans. The low cocaine content of the commercial wines and tonics explains why there were no reports of toxicity in the 1870s, even though the wines of Mariani in particular, and his many competitors in general, were wildly popular.

The benign phase of cocaine consumption abruptly came to an end in 1884, when Freud published his famous paper praising cocaine as a miracle drug[7]. A few months later, Koller discovered that cocaine was a local anaesthetic[8]. By the end of 1884, less than two months after Koller's paper had been read at the Heidelberg Ophthalmology Congress and less than five months after the publication of Freud's paper, cocaine production at Merck's factory in Darmstadt increased dramatically. Merck was at the time Europe's main cocaine producer, but in 1883 its total output was less than three-quarters of a pound (1.65 kg). Output increased to 3179 pounds in 1884, and to 158 352 pounds in 1886[9]. This increase in production was, of course, driven by increased demand. But it was also facilitated by an important technical advance—the introduction of semi-refined cocaine.

Coca leaves travel poorly, losing much of their cocaine content in transit. In 1885 a chemist working for Parke Davis, the largest American cocaine producer and Merck's fiercest competitor (Parke Davis even paid Sigmund Freud to endorse their brand of cocaine over Merck's) revolutionized the drug industry by devising a way to produce semi-refined cocaine on site[10]. Shipping and storage were simplified, prices fell, and the supply of semi-refined cocaine increased substantially.

When ample supplies of relatively inexpensive cocaine became available, patent drugmakers began adding very large amounts of purified cocaine to their products[11]. Vin Mariani may have contained only 6 mg cocaine per ounce, but competitors' products contained hundreds of milligrams per ounce. Not surprisingly, episodes of toxicity, and even deaths, soon became a regular feature of the *BMJ* and *The Lancet*. Matters were worsened by the advent of commercially manufactured hypodermic syringes at almost the same time.

Cocaine's addictive potential is at least partly related to blood concentrations. Within certain limits, an increase in the amount of cocaine administered increases the amount entering the bloodstream and ultimately the amount finding its way to the brain[12]. The rate of rise in concentration may be at least as important as the absolute concentration achieved in the brain, which is why smokable 'crack' cocaine has had such devastating results. Smoking a given amount of 'crack' cocaine results in a much higher blood concentration than snorting the same amount, and the peak level is reached much more quickly.

The explosion in cocaine use that occurred in America during the late 1980s is widely attributed to economic factors; crack was said to be much cheaper than powdered cocaine. There is no evidence to support this notion. Data from the US Drug Enforcement Agency suggest that prices for the two dosage forms are essentially the same[13]. A more plausible explanation would take into account the observation that 'crack' smoking offers higher brain concentrations more quickly.

Figures released by the US Government in 1996 show that the true price of cocaine has declined by nearly 75% during the past fifteen years; the sum required to buy

enough street drug to yield 1 g pure cocaine fell from $587 to $137[3]. The explanation is a glut of cocaine on the market. Policy makers and drug control experts seem blissfully unaware that the coca plant will grow nearly anywhere. South America is at present the main source; but during the 1800s, exports of coca from Java substantially exceeded those coming from South America. If blight eliminated South American coca production tomorrow, new suppliers in South East Asia could, and would, quickly make up any shortfall.

TOXICOLOGY OF COCAINE ABUSE

Patterns of drug abuse vary by location, but in most American jurisdictions, morphine, or ethanol, or both, are found in 30–40% of decedents where cocaine is deemed to be the cause of death[14]. Traces of other drugs, and adulterants, are commonly found in seized drugs and detected at necropsy, but these adulterants rarely seem to be a cause of toxicity[15].

The explanation has to do with the fact that most cocaine-related deaths occur in chronic, high-dose, cocaine users[16]. Toxicity in individual cases cannot be related to isolated measurements of cocaine or its metabolites, either in blood or in urine[17]. No specific cocaine blood concentration can be guaranteed to produce toxicity, just as no concentration of the drug can be guaranteed safe[18]. Tolerance to cocaine's vascular effects rapidly emerges, and chronic users may ingest huge amounts of drug with impunity[19]. On the other hand, chronic exposure to stimulant drugs (cocaine and methamphetamine) leads to changes in the heart that favour the occurrence of lethal arrhythmias (see below).

After death, cocaine is released from tissue depots and drug redistribution occurs[20]. The drug concentrations measured in post-mortem blood and tissue are site dependent[21] and are also a function of the post-mortem sampling interval, not to mention ambient temperature at the scene and the temperature at which the cadaver was stored[22]. These variables explain why post-mortem cocaine concentrations in cases where cocaine is the cause of death totally overlap concentrations in cases where cocaine was clearly not the cause of death (e.g. a homicide victim or a passenger in a car crash)[16].

MEDICAL CONSEQUENCES OF COCAINE ABUSE

Although there has been speculation that stimulant abuse, in some as yet uncharacterized fashion, increases the risk for homicide, suicide, and violent death in general, the fact remains that most cocaine-related deaths are a consequence of taking too much cocaine for too long a time. In large American cities, most cocaine-related deaths (roughly 60%) are a direct consequence of chronic cocaine toxicity. Homicides account for another 20%. Suicide is the manner of death in less than 10% of cases where cocaine is detected, and in those cases the presence of cocaine, or cocaine metabolites, is usually only an incidental finding[14,23].

Cocaine exerts its toxic effects in several different ways. In addition to blocking sodium channels, it prevents the reuptake of neurotransmitters such as dopamine, noradrenaline, adrenaline, and serotonin[24], thereby exaggerating the effects produced by those hormones. Cocaine also causes additional adrenaline to be released from the adrenals[25]. Sodium channel blockade, a feature common to all local anaesthetic agents, is probably only a factor in cases of massive overdose[26]. Suicidal overdoses have been reported[27], but most documented cases of massive overdose involve drug smugglers with a ruptured packet of cocaine in their intestines[28].

Small doses of cocaine delay repolarization and decrease cardiac output; massive doses can lead to cardiac standstill. As with any other local anaesthetic agent, administration of large doses of this drug will result in continuous seizure activity[29]; but, unlike other local anaesthetics, cocaine also affects temperature regulation[30], so that individuals with a cocaine overdose are always to some degree hyperthermic. Pulmonary and cerebral oedema are the principal findings at necropsy in such instances[31].

The remainder of cocaine-related deaths can be divided into four groups—stroke, excited delirium, myocardial infarction, and arrhythmic sudden cardiac death. Stroke is an uncommon occurrence, more often than not haemorrhagic and usually involving young adults[32] with pre-existing vascular malformations. Presumably, drug-induced hypertension leads to rupture of these malformations, although vasospasm might also be a factor. Excited delirium is a somewhat more frequent occurrence[33]. This disorder was first observed in hospitalized psychiatric patients more than 150 years ago[34]. Today most victims are chronic, long-term, high-dose stimulant abusers[35]. The syndrome is comprised of four elements that occur in sequence—hyperthermia, psychotic agitation, respiratory arrest, and death. This syndrome is not exclusive to cocaine users; it occurs also in abusers taking other stimulant drugs, in schizophrenic patients, and in patients taking neuroleptic medications. Hyperthermia is the result of dopamine receptor changes in the brainstem[35], while the psychotic behaviour results from up-regulation of kappa-2 receptors in the amygdala[36]. Whether similar changes account for the occasional case of paranoia seen in very heavy binge users, first described by the French neurologists Magnon and Saury in 1890, is not known[37].

Nor is it clear whether respiratory arrest is centrally mediated, or simply secondary to cardiac arrest. The justification for supposing the latter is that cocaine users with this disorder invariably have mildly to moderately

enlarged hearts[38], displaying the sort of microfocal myocardial fibrosis typically seen in patients with phaeochromocytoma and catecholamine toxicity[39]. Cardiac enlargement and myocardial fibrosis both favour the occurrence of sudden cardiac death.

While cases of stroke and excited delirium are sufficiently uncommon to be still reportable, cases of myocardial infarction are not. There are ample reasons why cocaine users should have myocardial infarcts. Cocaine raises blood pressure and thereby increases myocardial work[40]. Pre-existing but symptomless coronary artery disease may be rendered symptomatic, especially if the drug is used during any strenuous physical activity. Even in the absence of pre-existing coronary artery disease, there is evidence that cocaine can induce spasm of the large epicardial vessels[41] and that it also accelerates atheroma formation[42].

Sudden cardiac death is a frequent occurrence and probably accounts for most of the 7000 to 10 000 cocaine-related deaths reported in the USA each year[43]. Coronary artery disease is found in some cases, but more often than not the only cardiac abnormality evident is myocardial hypertrophy, with or without microfocal fibrosis. This increase in heart size may simply represent a physiological response to drug-induced increases in blood pressure, but some evidence also points to the activation of myocardial early genes[44].

Why should heart size be an independent predictor for sudden death? For one thing, it leads to QT dispersion[45], making re-entrant arrhythmias more likely[46]. Another reason is that in hypertrophied heart the endocardium is less well supplied with blood vessels and relatively ischaemic, which again makes the occurrence of lethal arrhthymias more likely. Myocardial fibrosis also favours QT dispersion, because collagenous scars disrupt the orderly progression of depolarization wave fronts. Cocaine-associated increases in heart size often go unnoticed at necropsy because many pathologists still do not relate the heart size to body weight. However, when nomograms for normal heart size are utilized, heart weights usually prove to be 10–15% greater than predicted for the individual's size[16,47].

CONCLUSIONS

Except in the very rare cases of massive overdose, cocaine associated deaths occur only in long-term chronic users. Chronic use leads to the formation of anatomical and neurochemical substrates that favour cardiovascular toxicity and sudden death. The number of deaths, and the incidence of certain specific cocaine-related syndromes, is an indicator of the drug supply. Substantial numbers of cocaine-related deaths only occur when cocaine is cheap and abundant. In the USA, the number of such deaths has increased in parallel with the drug supply over the past decade. Twenty years ago, excited delirium was a rare disorder in the United States, but that is no longer the case. Reports of excited delirium deaths in the UK indicate that European cocaine supplies are expanding.

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